Risks from Disinfection By-Products Produced by Chlorine, Chloramine, and Chlorine Dioxide

R.J. Bull

Disinfection and Disinfection By-product Symposium

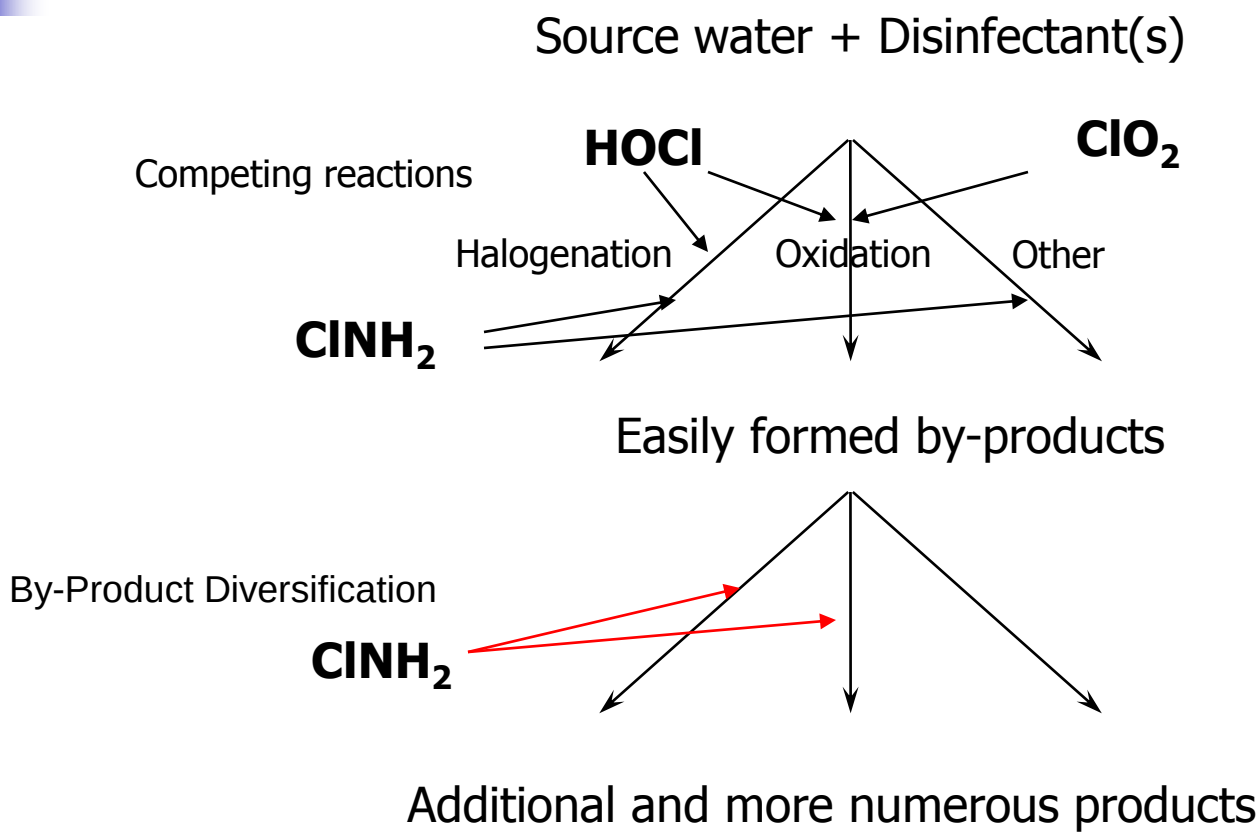
Vermont Agency of Natural Resources

11-01-07

Outline

- General scheme for by-product formation
- Nature of health effects associated with DBPs
- Discuss risks (i.e. probability of harm) from particular DBPs
- Associate risks with different uses of specific disinfectants
- Identifiable data gaps
- Discuss site-specific occurrence of precursors

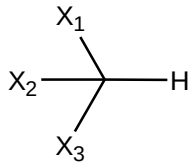
General scheme of By-product formation



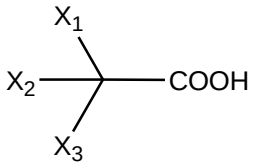
Structures

Oxyhalide anions: BrO^-_3; ClO^-_3; ClO^-_2; ClO^-

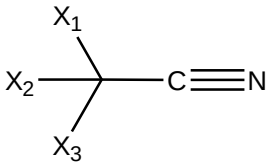
Chloramines: $ClNH_2$; Cl_2NH; Cl_3N



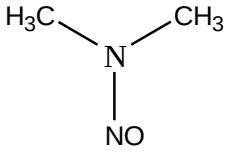
Trihalomethane
X = Br, Cl, I



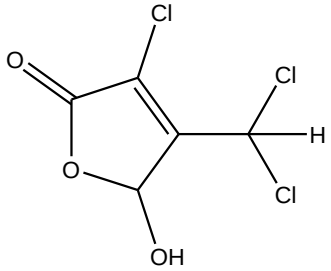
Haloacetic acids
X = Br, Cl, I, or H



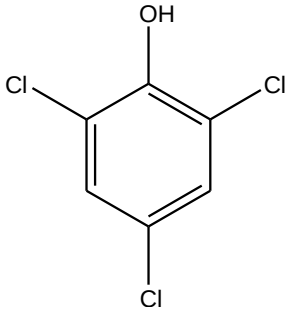
Haloacetonitriles
X = Br, Cl, I, or H



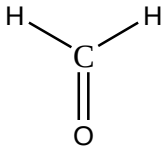
N-nitroso-N-dimethylamine
(NDMA)



3-Chloro-4-(Dichloromethyl)-
5-Hydroxy-2(5H) furanone **(MX)**



2,4,6-Trichlorophenol



Formaldehyde

Health Effects Associated with DBPs

- Cancer
- Reproductive
- Developmental effects
- Organ-specific toxicities
  - Hemolytic anemia – methemoglobinemia
  - Liver toxicity
  - Kidney toxicity
  - Neurotoxicity

Tools: Epidemiology

- Identify and measure effects at ambient exposure levels
  - Prospective
  - Retrospective – more common
- Methodology
  - Ecological studies – broad, but subject to severe confounding – not usually accepted as strong evidence because of generally poor exposure assessment – exception arsenic carcinogenesis
  - Case control studies – control confounding, but are focused on a single endpoint
- Little confidence in results of single studies – whether positive or negative.
  - Essential that observations be extended to other sites
  - Results are consistent among studies
  - Must make biological sense (i.e. inconsistencies with other information, e.g. toxicological information, dose-response relationships, etc)
- Difficult to establish cause and effect

Tools: Toxicology

- Primarily a predictive tool – based on data obtained with animal testing
- Focuses on single chemical or simple mixtures
- Establishing cause and effect much easier
- The point is to see an effect and establish a margin of safety
  - Doses used are usually much above those that will be encountered in the environment
- Use of data to predict human health effects requires extrapolation between species and to low dose
- Addressing some types of effects require very specific designs, not included in general toxicological testing
  - Hypersensitivity reactions, e.g. allergies

Cancer

- Epidemiological studies:
  - Consistent association of bladder cancer with chlorinated drinking water
  - Other cancer sites less consistent
- Toxicological studies have identified specific DBPs that cause cancer in animals
  - Trihalomethanes (THMs) – vehicle and method of admin issues – cannot replicate with treatments in drinking water
  - Haloacetic acids (HAAs) – Low dose extrapolation should be non-linear
  - Bromate – low dose extrapolation probably non-linear
  - 3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX)
  - Nitrosamines (NDMA, NDEA, nitrosopyrrolidine, nitrosomorpholine)
  - 2,4,6-Trichlorophenol
  - Chlorate
  - Formaldehyde, acetaldehyde, and benzaldehyde

Cancer is the largest documented risk

Risks of bladder cancer attributed to chlorinated drinking water

	Males	Females
Bladder Cancer Incidence	39/100,000†	10.1/100,000
Lifetime probability for developing bladder cancer	0.0356‡	0.0113‡
Population Attributable Risks to Cl_2 H_2O§	Cancer risk attributable to Cl_2 H_2O	
2%	0.0007	0.0002
17%	0.006	0.002

† Age adjusted incidence for years 1997-2001 (*3*)

‡ Years 1999-2001, (*3*)

§ (*1*)

Reproductive Effects

- Epidemiological studies:
  - Spontaneous abortion associated with chlorination by-products, but inconsistent or not confirmed by other studies
  - Stillbirths observed in other studies may be related, but those that find stillbirths find no evidence of spontaneous abortion
  - One study found sperm abnormalities associated with BDCM – weak association and unreplicated
  - Studies have only looked at chlorinated water
- Toxicological Studies
  - THMs – Effects seen at very high dose (50 mg/kg body weight) – inconsistent among strains – issues with vehicle and method of administration
  - HAAs – dihaloacetic acids – spermatogenesis
  - Haloacetonitriles – fetotoxic – issues with vehicle
  - Doses required to produce effects very high compared to amounts that would be obtained from chlorinated or chloraminated drinking water

Developmental effects: Epidemiology

- Associations of low birth weight for gestational age
  - Most consistent outcome
  - Causal agents have not been identified – THMs unlikely to cause
- Neural tube defects
  - Associated with THMs
  - THMs are not plausible causes
- Other disinfectants have received little or no study

Developmental effects

- Evidence of cardiac abnormalities with high doses of HAAs and HANs
- Evidence of developmental effects seen with dihaloacetic acids (i.e. DCA, BCA, and DBA) in embryo culture at very high concentrations. Unlikely to be relevant at concentrations produced in drinking water
- Several DBPs have the potential of affecting iodide uptake by the thyroid.
  - Chlorate – direct inhibition of iodide transport
  - Bromate - less important than its carcinogenic effects
  - Haloacetonitriles – conversion to cyanide, then to thiocyanate
  - Cyanogen chloride, cyanogen bromide – also via thiocyanate
- Impaired thyroid function has implications for brain development. Most critical among DBPs is chlorate, but it has not been has not been evaluated for developmental effects
- Chlorine dioxide appears to have some effects on brain development that are independent of any effect on the thyroid

Oxidative damage to red blood cells

- Limited epidemiologic data examining oxidative damage to red blood cells (anemia or methemoglobinemia) – no associations
- Clinical studies appear to indicate little harm at typical concentrations of oxyhalide anions (i.e. chlorate, chlorite, hypochlorite, chlorine dioxide, and chloramine) even in sensitive individuals
- Toxicological studies identify effects at high dose for chlorite, chlorate, bromate, hypochlorite and chloramine. Do not appear of concern at MCL concentrations

Organ-specific toxicities cont.

- Liver toxicity
  - THMs identified both clinically & animal studies – also target for cancer, but controlled at the MCLs
  - HAAs – Clinical & animal studies demonstrate effect – also major target for cancer, but controlled at the MCL
- Kidney toxicity
  - THMs similar to liver – controlled at the MCL
- Stomach
  - Target for formaldehyde & acetaldehyde at very high oral doses – not relevant at concentrations that are produced in disinfection of drinking water
- Lung
  - Also a target of formaldehyde. Could be an issue in showers. At 100 µg/L not an issue.
- Neurotoxicity
  - Peripheral neuropathy and CNS effects produced by DCA at high doses, not a critical effect – liver effects occur at lower dose

Unresolved issues/data needs

- Threshold of respiratory irritation
  - Effects of chlorine well known and thresholds documented, although not addressed in regulation
  - Chloramines more potent
    - not addressed in regulation
    - Evidence of chronic respiratory disease in lifeguards and food workers
  - In skin hyperplasia study, mice had to be protected from chlorine dioxide or chloramine: Died from acute respiratory irritation when swimming in the water. Chlorine did not produce the effect up to 1000 ppm
  - Rats inhalation of fumes from drinking water as low as 25 ppm ClO_2 in rats producing inflammation, hyperplasia & metaplasia in nasal turbinates

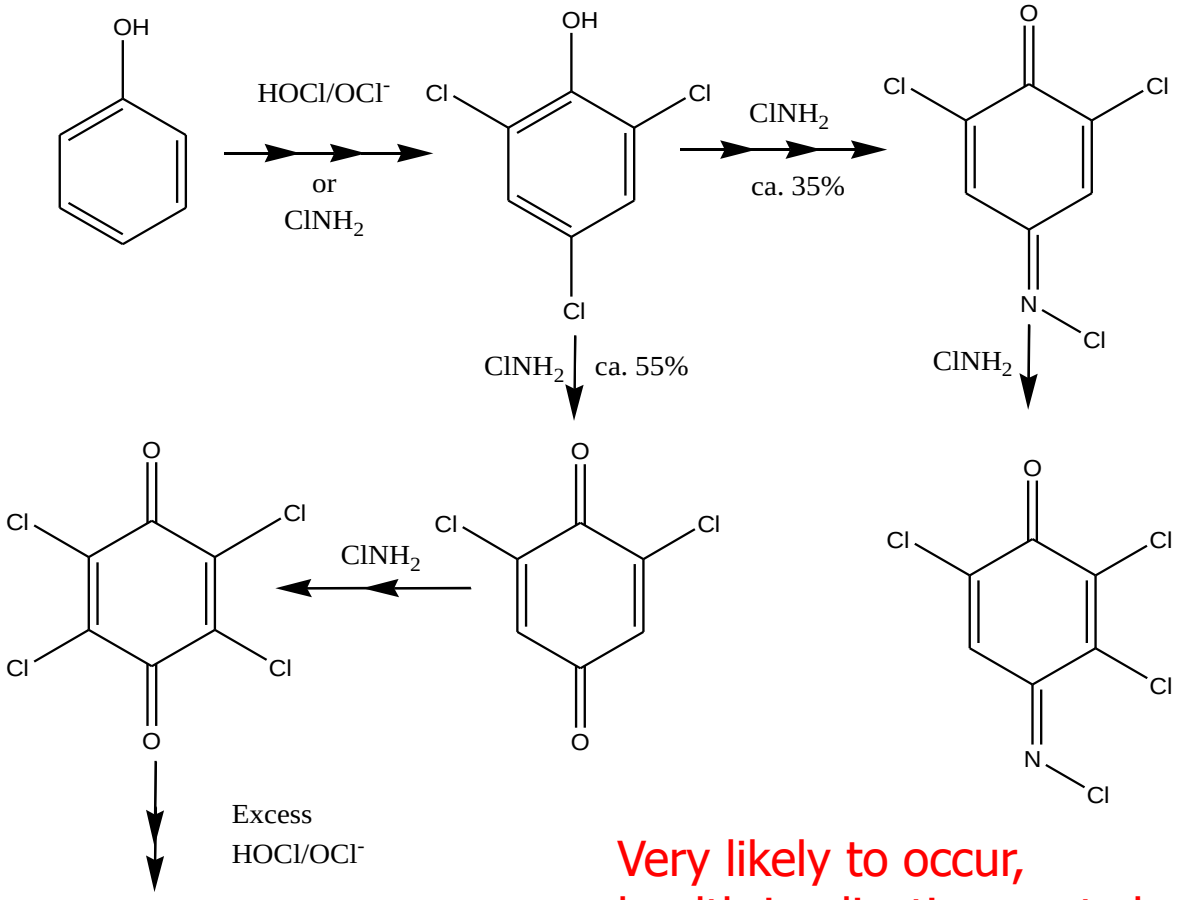
Unresolved issues/data needs

- Toxicology of most DBPs unknown
  - Because of low concentrations most are of little concern
  - However, some are now being discovered that are quite potent (e.g. NDMA)
  - Potency of regulated DBPs insufficient to account for a cancer risk of the magnitude seen in epidemiology studies of chlorinated water – if real other by-products have to be responsible
  - Same issue with reproductive/developmental effects – however, data are much less consistent

Unresolved issues/data needs

- Major DBPs (i.e. found at > 10 µg/L) lack data
  - Organic N-chloramines
- Minor DBPs of potential toxicological significance if present at low concentrations
  - N-dialkylnitrosamine formation with natural alkaloids – e.g. 3-methylindole a microbial metabolite of tryptophan (Chloramine)
  - Cyclo-pentenoic acid derivatives (Chlorine)
  - Furanone derivatives related to MX (Chlorine)
  - Haloquinones (Chloramine)
- Effects of chlorate on brain development have not been assessed (primarily associated with use of hypochlorite solutions)

An example of a data gap relevant to a switch from chlorine to chloramines as the residual disinfectant



Haloacids, THMs, other aliphatic products

Very likely to occur, health implications not clear

DBPs as complex mixtures: Are THMs good surrogates?

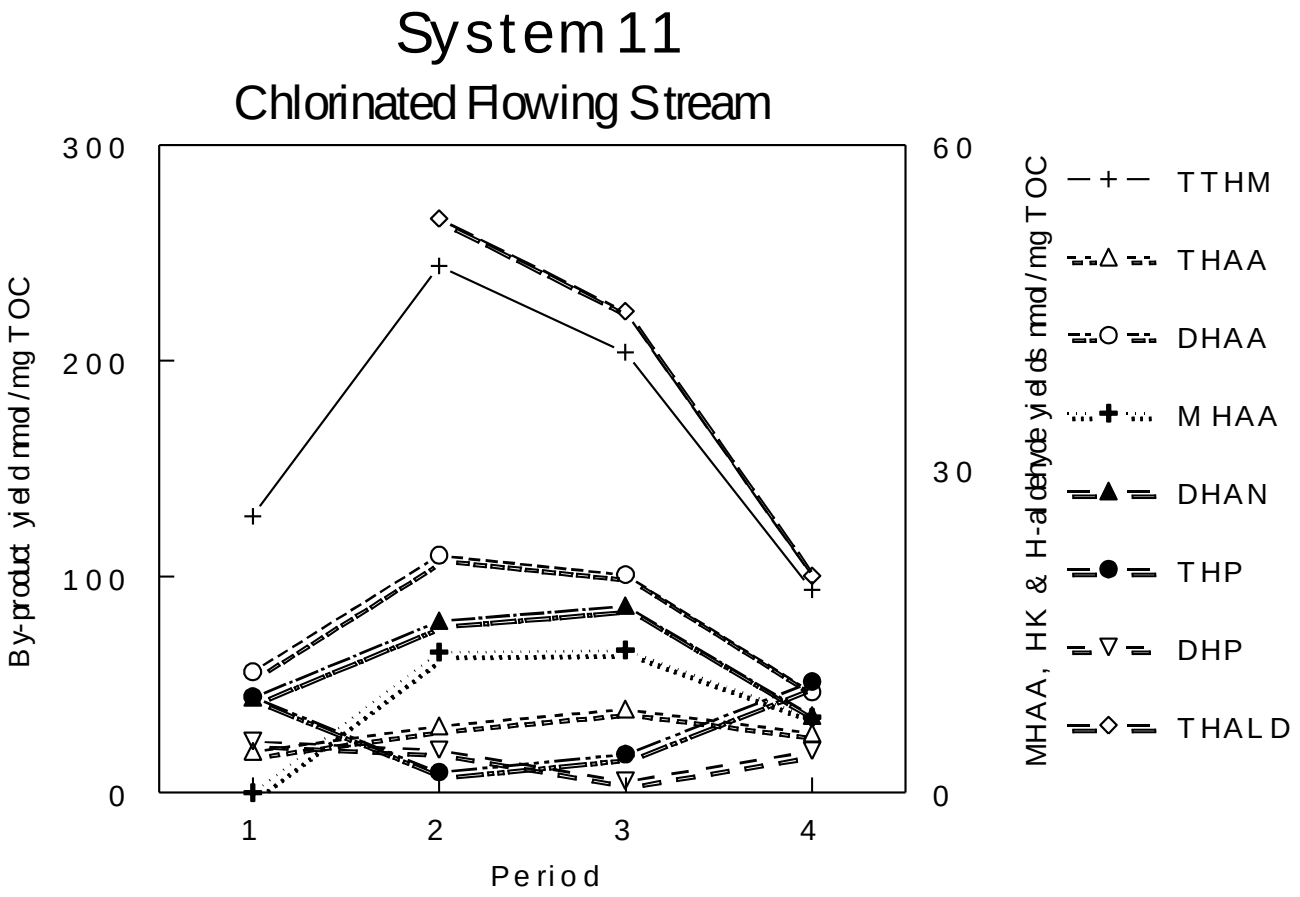
Correlation in concentrations of chlorinated by-products by treatment and source[a]

Base DBP	Correlate	All Cl_2	Cl_2 GW	Cl_2 LR	Cl_2 FS	All $ClNH_2$	$ClNH_2$ LR	$ClNH_2$ FS
Chloroform	TCAA	0.73	1.0	0.59	0.75	0.91	0.98	0.83
	TCAA+CH	0.82	0.99	0.74	0.86	0.92	0.99	0.93
	DCAA	0.83	0.99	0.60	0.92	0.87	0.85	0.90
	DCAN	0.77	0.99	0.54	0.72	0.72	0.96	**0.31**
	CP	0.67				**0.31**		
	TCP	**0.33**	0.98	0.42	**0.33**	0.58	0.92	**0.16**[b]
	DCP	**0.23**	0.78	**0.056**	**0.31**	0.35	0.57	**0.12**

[a] All Cl_2 is inclusive of all chlorinated supplies, and all $ClNH_2$ of all chloraminated systems. GW indicates ground water, LR indicates lake and reservoir water, and FS flowing streams Data taken from USEPA/AMWA study of 35 utilities, 1989

[b] .Black type = positive correlation, Red font represents negative correlation

Seasonal relationship among DBPs in one supply



Summary of Health Concerns with Chlorinated Water: Epidemiology

General concern	Specific Concern	Major correlates
Cancer	Bladder	Chlorinated water, THMs
	Colon, rectum	Chlorinated water, but inconsistent among studies
Reproductive effects	Spontaneous abortion	THMs, BDCM, **TOX**
	Small for Gestational Age (SGA)	Chlorinated water, THMs
	Neural tube defects	Chlorinated water, THMs

Summary of Health Concerns with Chlorinated Water: Toxicology

Cancer	Liver	TCM, BDCM, DBCM, HAAs
	Kidney	TCM, BDCM
	Colon	BDCM, TBM
	Thyroid	MX, Chlorate
Reproductive effects	Total litter resorption	BDCM
	Spermatogenesis	DHAAs
Developmental effects	Teratogenesis	HAAs, HANs
	Brain development	Chlorate?
General Toxicity	Liver	THMs, HAAs
	Kidney	THMs

Summary of Health Concerns with Chloraminated Water: Epidemiology

General concern	Specific Concern	Major correlates
Cancer	Bladder – decreased risk relative to chlorinated water	Not clear
	Other organs	Not studied
Reproductive effects	Spontaneous abortion	Not studied
	Small for Gestational Age (SGA)	Not studied
	Neural tube defects	Not studied

Summary of Health Concerns with Chloraminated Water: Toxicology

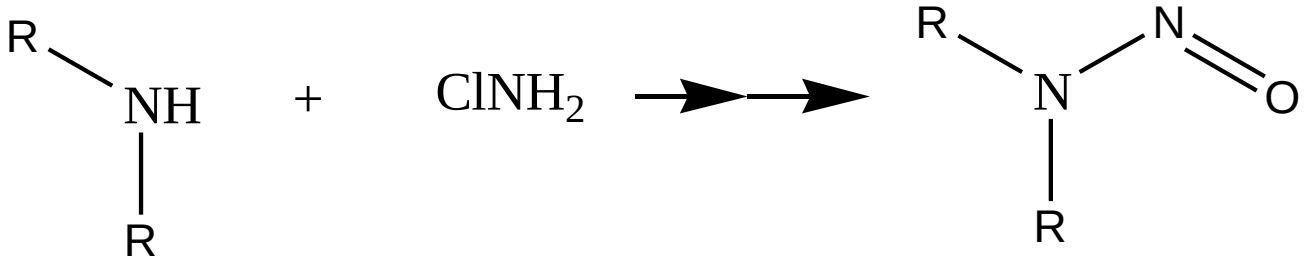
Cancer	Liver	TCM, BDCM, DBCM, HAAs, **NDMA**
	Kidney	TCM, BDCM
	Colon	BDCM, TBM
	Thyroid	MX, Chlorate
Reproductive effects	Total litter resorption	BDCM
	Spermatogenesis	DHAAs
Developmental effects	Teratogenesis	HAAs, HANs
	Brain development	Chlorate?
General Toxicity	Liver	THMs, HAAs
	Kidney	THMs

Summary of toxicological evaluations for Chlorine Dioxide

Effects Evaluated	**ClO_2**	**ClO_2^-**	**ClO_3^-**
Subchronic toxicity	**CE**	MR	MR
Carcinogenicity	NS	MR	NE
Oxidative damage:			
Methemoglobinemia	MR	CE?	PS
Anemia	MR	**CE**	MR
DNA damage	MR	MR	MR
Endocrine effects			
Inhibition of NIS	MR	MR	**CE**
Reproductive effects	**CE**	MR	NS
Developmental effects	**CE**	MR	NS

CE = critical effect, MR = minimal risk, NE = not evaluated, NS = not studied, PS = pot. synergism

Example of site-specific precursors: Nitrosamine formation



Dialkylamine Chloramine Dialkylnitrosamine

General Conclusions (1)

- Epidemiological data project the highest consistent risk – bladder cancer – with chlorinated water
  - Epidemiological data indicate this risk is reduced by chloramination or ozone
  - Data has not been extended to other target organs or effects
- Reproductive effects could be of concern with chlorination, but results have been inconsistent or unreplicated
  - There are no epidemiological studies with chloramination
- Associations do not identify the causes
  - Very unlikely that causal agents can be identified epidemiologically
  - Case control designs focus on single endpoints
  - Cannot rule out effects on other endpoints by other disinfectants

General Conclusions (2)

- Toxicological data demonstrate that DBPs can produce adverse effects in animals at very high doses compared to doses obtained from drinking water
- High degree of uncertainty as data are extrapolated between species or to low dose
- These risks have been largely addressed/controlled by development of appropriate MCLs with adequate margins of safety.
- Knowledge about toxicological effects of DBPs is limited to a small number of DBPs –
  - Therefore, lack of low dose effects does not directly refute epidemiological data

General conclusions (3)

- Formation of nitrosamines is a risk largely specific to chloramines
- Dialkylnitrosamines are about 1000-10,000 more potent as carcinogens than the THMs and HAAs
- Only formed when appropriate precursors are present
  - Occur in the ng/L range unless there are sources of the dialkylamines that can serve as precursors
- This is a problem that can be easily addressed by appropriate analysis of the treated water

General conclusions (4)

- From a health effects perspective the focus on THM and HAA formation as indicators of risk from DBPs not justified by data
  - Not really plausible causes of health effects
  - They are not mutagenic carcinogens
  - Positive results obtained when corn oil was the vehicle have not been confirmed when the similar doses are given in drinking water
  - Controlling formation of THMs and HAAs can lead to increased concentrations of intermediates in their formation which may actually be more toxic/carcinogenic
  - Their concentrations do not vary dependably with other DBPs, even halogenated DBPs